Original Article

Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age

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What is already known about this topic? Severe asthma has distinct phenotypic features in childhood, but whether the features of severe asthma are different with age has not been widely studied.

What does this article add to our knowledge? With advancing age, asthma is more prevalent in women than men, and is associated with higher body mass index and greater airflow limitation, but lower markers of Th2 inflammation.

How does this study impact current management guidelines? Alternate therapies targeting non-Th2 mechanisms of inflammation need further study in the management of adult patients with severe asthma.

BACKGROUND: The effect of age on asthma severity is poorly understood.
OBJECTIVES: The objective of this study was to compare the baseline features of severe and nonsevere asthma in the Severe Asthma Research Program (SARP) III cohort, and examine in cross section the effects of age on those features.
METHODS: SARP III is a National Institutes of Health/National Heart Lung Blood Institute multisite 3-year cohort study conducted to investigate mechanisms of severe asthma. The sample included 188 children (111 severe, 77 nonsevere) and 526 adults (313 severe, 213 nonsevere) characterized for demographic features, symptoms, health care utilization, lung function, and inflammatory markers compared by age and severity.
RESULTS: Compared with children with nonsevere asthma, children with severe asthma had more symptoms and more historical exacerbations, but no difference in body weight, post-bronchodilator lung function, or inflammatory markers. After childhood, and increasing with age, the cohort had a higher proportion of women, less allergen sensitization, and overall

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Abbreviations used

BD- Bronchodilator
BMI- Body mass index
DCC- Data coordinating center
FeNO- Fraction expired nitric oxide
FEV_1- Forced expired volume in 1 second
FEV_1/FVC- Forced expired volume in 1 second/forced vital capacity ratio
FVC- Forced vital capacity
NHLBI- National Heart Lung Blood Institute
NIH- National Institutes of Health
SARP- Severe Asthma Research Program

fewer blood eosinophils. Enrollment of participants with severe asthma was highest in middle-aged adults, who were older, more obese, with greater airflow limitation and higher blood eosinophils, but less allergen sensitization than adults with nonsevere asthma.

CONCLUSIONS: The phenotypic features of asthma differ by severity and with advancing age. With advancing age, patients with severe asthma are more obese, have greater airflow limitation, less allergen sensitization, and variable type 2 inflammation. Novel mechanisms besides type 2 inflammatory pathways may inform the severe asthma phenotype with advancing age. **© 2017 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).** **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Severe asthma; Asthma phenotypes*

Patients with severe asthma require treatment with high-dose inhaled corticosteroids plus a second controller to maintain symptom control or have uncontrolled asthma despite therapy.[1] Although these patients are estimated to represent 5% to 10% of the total asthma population in the United States, they have frequent exacerbations, impaired quality of life, and account for more than half of the annual costs of asthma.[2] From 2001 to 2012 the National Institutes of Health/National Heart Lung Blood Institute (NIH/NHLBI) supported the Severe Asthma Research Program (SARP) I and II cohorts to study mechanisms differentiating severe from nonsevere asthma.[3-7] SARP investigators characterized severe asthma as a heterogeneous syndrome with diverse molecular, biochemical, and cellular inflammatory features and structure-function abnormalities.[7] Adults and children with severe asthma were further categorized by unbiased statistical methods into clusters based on distinguishing clinical features.[5,6] Although older age was a determinant of treatment failure in patients with asthma participating in the NIH Asthma Clinical Research Network therapeutic trials, these interventional studies did not target participants with severe asthma.[8] Furthermore, age-related differences in the features of asthma were not studied in the original SARP I and II cohorts.

In November 2012, the NIH/NHLBI formed SARP III, a network of US investigators and a data coordinating center (DCC) located at regional academic health centers involved in severe asthma research. The main objective of SARP III is to advance understanding of severe asthma through the integration of mechanistic studies with detailed phenotypic characterization. To accomplish this goal, a cohort of adults and children with severe and nonsevere asthma was recruited for detailed characterization and enrollment into an observational study. This report highlights the baseline demographic, clinical, physiologic, and inflammatory features of participants with severe compared with nonsevere asthma and how these differences are influenced by age. The selection of specific features to examine with age was exploratory to generate hypotheses to be tested further in the longitudinal protocol.

METHODS

SARP clinical centers were tasked by NIH/NHLBI to recruit a sample that included 60% severe asthmatics, 50% women, 30% non-white minorities, and 25% children. Details of the screening and enrollment procedures are provided in a consort plot (Figure 1) and in the Methods section and Tables E1 and E2 in this article's Online Repository at www.jacionline.org. Current tobacco smokers

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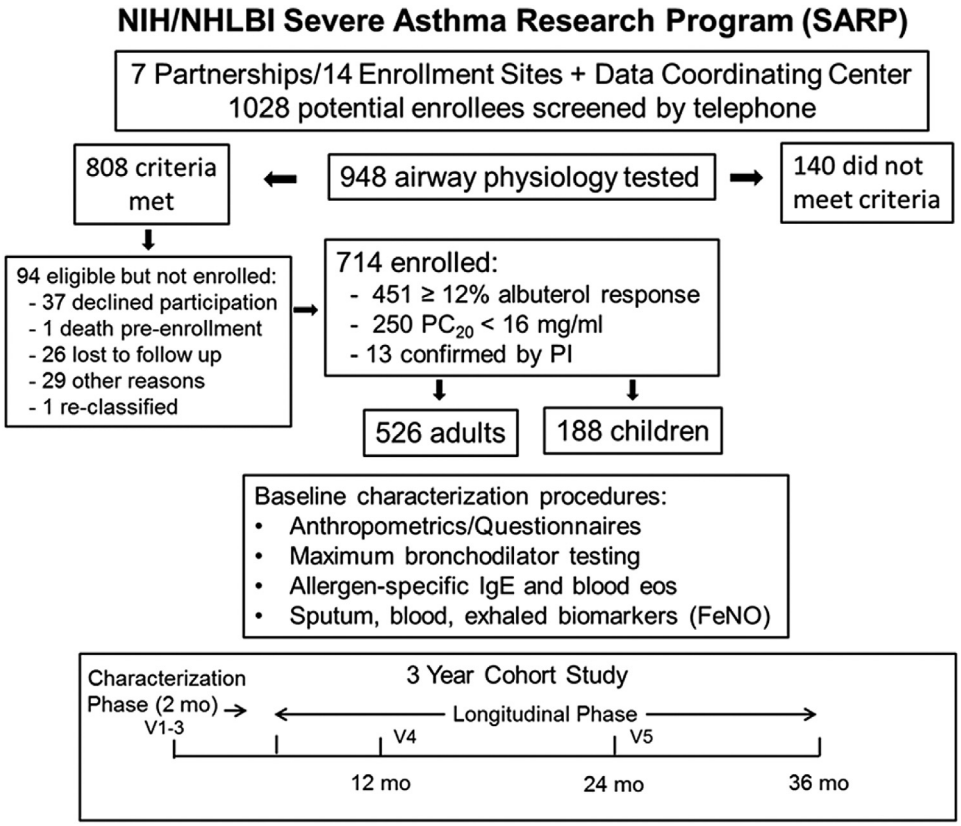

FIGURE 1. SARP III screening, consort procedures, characterization procedures, and schematic of the longitudinal cohort study. Potential enrollees who did not complete the initial screening questionnaire are not counted among the 948 who underwent airway physiology screen testing. Potential enrollees with more than 1 screen failure are also not included. *FeNO*, Fraction expired nitric oxide; *NIH/NHLBI*, National Institutes of Health/National Heart Lung Blood Institute; *SARP*, Severe Asthma Research Program.

and those with significant past smoking history (>5 pack years if they were <30 years of age and >10 pack years if they were >30 years of age) were excluded. Participants maintained medications for asthma as prescribed by their care provider. Study procedures were approved by the Institution Review Board at each institution and an independent Data Safety Monitoring Board. All subjects provided informed consent and/or assent.

Asthma was confirmed based on responsiveness to β-agonist (≥12% increase in forced expired volume in 1 second [FEV_1] from baseline post-albuterol, n = 451) or (if <12%), a positive methacholine bronchoprovocation (n = 250). Thirteen enrollees with an FEV_1 <50% predicted, and an albuterol response <12% did not undergo methacholine bronchoprovocation. Severe asthma was defined according to a modification of the European Respiratory Society/American Thoracic Society consensus definition.[1] Thresholds for high-dose inhaled corticosteroid therapy were ≥440 mcg of fluticasone equivalents per day for children 6-11 years of age and ≥880 mcg fluticasone equivalents per day for subjects 12 years of age and older. Enrollees treated with high-dose inhaled corticosteroids for at least 6 of the previous 12 months and the 3 months before enrollment were assigned to the severe subgroup and those who did not meet criteria for severe asthma were assigned to the nonsevere subgroup. "Children" were defined as those participants <18 years of age at enrollment.

Characterization procedures, adapted from SARP I and II,[3-6] included history and physical examination, vital signs, height, weight, and Tanner staging for children, characterization questionnaires, assessment of 1-week (Asthma control quotient, 6-item) and 4-week (Asthma Control Test, Childhood Asthma Control Test) symptom control, asthma-related quality of life scales (standardized Asthma Quality of Life Questionnaire and Pediatric Asthma Quality of Life Questionnaire), spirometry with maximal β-agonist reversibility testing (dose escalation protocol at 180 mcg albuterol increments up to 720 mcg), sputum induction (age 12 and older), exhaled nitric oxide (FeNO), and blood for complete blood count, total IgE, and allergen-specific IgE. Quality standards for spirometry were followed at each site, and results audited through the DCC. Medication adherence was measured by the Medication Adherence Report Scale.[9]

Data analysis

These included sex, body mass index (BMI), prevalence of obesity (defined as a BMI ≥ 30 kg/m^2 for adults and > 95th percentile for children), pre- and maximum post-bronchodilator (BD) lung function and prevalence of airflow limitation (FEV_1/forced vital capacity [FVC] ratio ≤ lower limit of normal of the Global Lung Initiative reference values),[10] maximum FEV_1 BD response (both as absolute change and % change in FEV_1 % predicted from baseline), prevalence of allergen sensitization, total blood eosinophil count, and FeNO. Allergen sensitization was defined as an elevated IgE (>0.35 IU/mL) to one of 15 allergen-specific IgE blood tests (Methods section in this article's Online Repository at www.jacionline.org).

Multiple sensitization was defined as ≥4 positive specific IgE tests, determined by the median of the number of positive blood allergen tests in the sample. The criterion for peripheral blood eosinophilia was ≥300 cells/μL,[11] and for increased FeNO ≥30 ppb.[12,13]

The cohort features were stratified by asthma severity (severe and nonsevere) and age group (children <18 years and adults ≥18 years). Nonsevere asthma was classified as mild intermittent, mild persistent, and moderate persistent (both treated and not treated with inhaled corticosteroids; Table E3, available in this article's Online Repository at www.jacionline.org). The features of ineligible versus enrolled participants in the study sample are provided (Table E4, available in this article's Online Repository at www.jacionline.org).

Categorical data are presented as count and percentages grouped according to severe versus nonsevere and tested with the Pearson χ^2 test. Continuous data with approximately Gaussian distributions are presented as mean and standard deviation, and differences by severity tested with a *t*-test. Continuous data with skewed distributions are presented as median and quartiles and differences by severity tested with a Wilcoxon rank sum test. Supplemental analyses with and without 13 participants with (a) FEV_1 < 50% predicted, (b) enrollees with a maximum BD response <12.5% from baseline, and (c) enrollees who did not undergo methacholine bronchoprovocation tests were compared. The analysis results did not differ when these subgroups were excluded.

The relationship between age of enrollment and specific outcomes was modeled using cubic splines with appropriate distribution and link functions. In conducting the analysis, age at enrollment instead of duration of asthma was used as a dependent variable because duration of asthma does not correlate with risk factors for severity and is limited by recall bias.[14] Continuous outcomes with the Gaussian distribution utilized the normal distribution with identity link, binary outcomes utilized the binomial distribution with logit link, and count outcomes utilized the Poisson distribution with log link. In addition to age, models also included severity and the interaction between age and severity to determine whether the shape of the age relationship differed by severity. *P* values of <.05 indicated statistical significance. Whereas the selection of the outcomes of interest was exploratory and not based on *a priori* hypotheses, no adjustment was made for multiple tests. All summary statistics, analyses, and graphs were performed via SAS/STAT and SAS/GRAPH software, Version 9.4, of the SAS System for Windows, Copyright 2012 SAS Institute, Cary, NC.

RESULTS

Differences between severe and nonsevere asthma

Children

General features. Approximately 26.3% of the cohort were children <18 years of age (n = 111 severe; n = 77 nonsevere) (Table I). The percentage of males exceeded females, and more African American children (42%) were enrolled compared with adults (25%). Children with severe asthma had more symptoms and historical exacerbations, lower quality of life, and (by definition) took more controller medications and prednisone than children with nonsevere asthma, but were no more obese. There was no significant difference in age at diagnosis of asthma or duration of asthma by severity in children. Mean medication adherence scores in children did not differ by asthma severity.

Lung function. Children with severe asthma had greater pre-BD airflow limitation than children with nonsevere asthma, but post-BD airflow limitation was similar in severe and nonsevere asthma (Table II). The mean post-BD absolute change in FEV_1 % predicted was significantly greater in children with severe asthma.

Inflammatory markers and allergen sensitization. No inflammatory marker, neither blood or sputum eosinophils nor exhaled NO, was higher in children with severe asthma (Table III). Likewise, total serum IgE and the degree of allergen sensitization did not differ in children based on asthma severity.

Adults

General features. Adults with severe (n = 313) and nonsevere (n = 213) asthma had similar proportions of female and minority participants (Table I). Adults with severe asthma were significantly older, more likely to have a higher BMI, more symptoms, and had more historical exacerbations, longer duration of asthma, and lower quality of life despite treatment with higher doses of corticosteroids. Adherence to treatment and age at diagnosis did not differ by severity.

Lung function. Adults with severe asthma had greater pre- and post-BD airflow limitation than adults with nonsevere asthma (Table II). The mean post-BD absolute change in FEV_1 % predicted was significantly greater in adults with severe asthma.

Inflammatory markers and allergen sensitization. Adults with severe asthma had similar values for total and differential cell counts in induced sputum compared with adults with nonsevere asthma, but adults with nonsevere asthma had higher exhaled NO levels than severe asthma (Table III). Adults with severe asthma had higher total blood eosinophil counts and a higher prevalence of blood eosinophilia (>300 cells/μL) than adults with nonsevere asthma. Although total serum IgE levels did not differ significantly based on asthma severity, enrollees with severe asthma had a significantly lower number of positive allergen-specific IgE blood tests.

Effects of age on the features of asthma

Asthma severity. After 18 years of age, the number of enrollees with severe asthma was higher and peaked in middle age between 50 and 55 years (Figure 2). In contrast, the number of enrollees with nonsevere asthma did not change appreciably after childhood. The distribution by age for adults with severe asthma differed from those with nonsevere asthma ($P = .002$).

Sex ratio. Before pubescence the ratio of boys to girls favored boys, but from young adulthood onward, the ratio of women was higher than men for both severe and nonsevere asthma ($P < .0001$; Figure 3).

BMI and obesity. From childhood to middle age, BMI was higher regardless of asthma severity, and was lower from 50 years of age onward ($P < .0001$; Figure E1, available in this article's Online Repository at www.jacionline.org). Accordingly, the prevalence of obesity followed a similar pattern with advancing age ($P < .0001$; Figure 4), which likewise was no different based on severity.

Lung function. Both the pre- and post-BD FEV_1/FVC % predicted were lower as age increased ($P < .05$ for both; Figure E2, *A* and *B*, available in this article's Online Repository

TABLE I. Features of the SARP III cohort by age and asthma severity: demographics, anthropometrics, smoking history, asthma control, quality of life, medication adherence, and treatment

	Children (<18 y)		Adults	
	Severe	Nonsevere	Severe	Nonsevere
Sample, n	111	77	313	213
Age at enrollment (y), mean ± SD	11.5 ± 2.8	11.6 ± 2.9	49.7 ± 12.8*	44.5 ± 14.6
Female, n (%)†	44 (39.6)	27 (35.1)	210 (67.1)	142 (66.7)
Race/ethnicity, n (%)				
Caucasian	39 (35.1)	33 (42.9)	194 (62.0)	142 (66.7)
African American	49 (44.1)	32 (41.6)	85 (27.2)	47 (22.1)
Other	23 (20.7)	12 (15.6)	34 (10.9)	24 (11.3)
Hispanic	17 (15.3)	11 (14.3)	10 (3.2)	9 (4.2)
Non-Hispanic	94 (84.7)	66 (85.7)	303 (96.8)	204 (95.8)
BMI (kg/m^2), mean ± SD	23.3 ± 6.5	22.3 ± 5.8	33.5 ± 8.5*	31.0 ± 7.9
Obese				
BMI ≥ 30 (18+ y) or BMI ≥ 95th percentile (<18 y), n (%)	42 (37.8)	23 (29.9)	195* (62.1)	96 (45.1)
Smoking history in adults ≥30 y (pack years), mean ± SD	n/a	n/a	0.9 ± 2.2	0.5 ± 1.5
Asthma symptom control				
ACT ≤ 19 (≥12 y), n (%)	29* (72.5)	8 (26.7)	240* (76.7)	90 (42.3)
cACT ≤ 19 (age 6-11), n (%)	51 (71.8)*	18 (38.3)	n/a	n/a
ACQ(6), mean ± SD	1.3 ± 0.9*	0.9 ± 0.8	1.9 ± 1.1*	1.1 ± 0.9
Age of asthma diagnosis (y), mean ± SD	3.0 ± 2.7	3.2 ± 2.8	20.1 ± 16.5	19.0 ± 15.3
Years since onset of asthma symptoms, mean ± SD	8.4 ± 3.4	8.4 ± 3.8	29.7 ± 15.6*	25.4 ± 15.6
Years since asthma diagnosis, mean ± SD	9.1 ± 3.2	9.3 ± 3.4	32.3 ± 15.7*	28.1 ± 15.9
Number of exacerbations, mean ± SD (past 12 mo)	2.8 ± 2.9*	0.8 ±1.0	2.3 ± 2.8*	0.6 ±1.2
Total AQLQ(S) score (≥12 y), mean ± SD	n/a	n/a	4.6 ± 1.3*	5.5 ± 1.1
Total PAQLQ(S) (age 6-11), mean ± SD	4.9 ± 1.3	5.8 ± 1.1	n/a	n/a
Number controller medications, median (IQR)	3.0 (2.0, 3.0)*	2.0 (1.0, 2.0)	3.0 (2.0, 4.0)*	2.0 (1.0, 2.0)
Daily oral corticosteroids current, n (%)	15 (13.5)*	1 (1.3)	70 (22.4)*	1 (0.5)
Medication Adherence Report Scale (MARS-5)‡, mean ± SD	21.9 ± 2.9	21.4 ± 3.7	22.4 ± 2.6*	21.4 ± 3.8

ACQ(6), Asthma control quotient, 6-item; *ACT*, Asthma Control Test; *AQLQ(S)*, standardized Asthma Quality of Life Questionnaire; *BMI*, body mass index; *cACT*, Childhood Asthma Control Test; *IQR*, interquartile range; *PAQLQ(S)*, standardized Pediatric Asthma Quality of Life Questionnaire; *SARP*, Severe Asthma Research Program; *SD*, standard deviation.

*$P < .05$ severe vs nonsevere.

†% per column.

‡Range 5-25.[9]

at www.jacionline.org), but the percentage of enrollees who met the definition of pre-BD airflow limitation was not different with age ($P = .60$; Figure 5, *A*). In contrast, the percentage of enrollees with post-BD airflow limitation was higher with age ($P < .001$; Figure 5, *B*). The maximum absolute change in FEV_1 % predicted post-BD was lower with age ($P < .0001$; Figure 6).

Inflammatory markers and allergen sensitization.

Whereas peripheral blood eosinophil counts were approximately 50% higher in children than adults, blood eosinophilia was lower by middle age but then was higher in late-middle-aged enrollees ($P < .0001$; Figure 7, *A*). Removing participants who took oral prednisone (n = 102; 96 severe, 6 nonsevere) from the analysis had no effect on differences in blood eosinophilia with age. Exhaled NO values were significantly lower with age ($P < .0001$; Figure E3, available in this article's Online Repository at www.jacionline.org). Children had significantly greater number of positive allergen-specific IgE blood tests than adults ($P < .0001$, Figure 7, *B*), and accordingly, serum IgE levels in children were 3- to 4-fold higher than adults ($P < .0001$; Figure E4, available in this article's Online Repository at www.jacionline.org).

Adherence.

Adherence to treatment was not different with age.

Interaction of age and asthma severity on specific outcomes

The interaction of age and asthma severity was significant for 3 outcomes. The absolute BD response and prevalence of sensitization to 4 or more allergens were both significantly lower with age in severe than in nonsevere asthma. Likewise, although exhaled FeNO levels were lower with age for the entire sample, exhaled NO values in severe asthma were relatively flat with age compared with the sharp decline from 20 to 50 years of age in FeNO in nonsevere asthma ($P < .0001$).

DISCUSSION

We report herein on the baseline characteristics of the SARP III cohort, a unique sample recruited according to prespecified demographic features at academic health centers concentrated in urban settings. Thus the sample is enriched in patients with severe asthma, women, and non-white minorities. In this report, we compare the baseline features of severe and nonsevere asthma

TABLE II. Features of the SARP III cohort by age and asthma severity: lung function and maximum bronchodilator response

	Children (<18 y)		Adults	
	Severe	Nonsevere	Severe	Nonsevere
Sample, n	111	77	313	213
Pre-BD FEV_1 (% pred.), mean ± SD	89.3 ± 18.5*	95.7 ± 14.8	68.9 ± 21.4*	85.8 ± 17.7
Mean *Z* score†	−0.8 ± 1.4*	−0.3 ± 1.2	−2.1 ± 1.4*	−1.0 ± 1.3
Pre-BD FVC (% pred.), mean ± SD	104.2 ± 16.7	108.3 ± 14.2	83.3 ± 18.4*	98.0 ± 16.9
Mean *Z* score	0.4 ± 1.4	0.7 ± 1.2	−1.2 ± 1.4*	−0.1 ± 1.3
Pre-BD FEV_1/FVC (% pred.), mean ± SD	85.0 ± 11.0	88.1 ± 9.6	81.2 ± 13.8*	87.3 ± 10.3
Mean *Z* score	−1.8 ± 1.2	−1.5 ± 1.1	−2.1 ± 1.4*	−1.5 ± 1.2
Pre-BD FEV_1/FVC < LLN‡, n (%)	66* (59.5)	33 (42.9)	194* (61.8)	96 (45.1)
Maximum post-BD FEV_1 (% pred.), mean ± SD	105.7 ± 18.0	108.4 ± 13.6	81.4 ± 20.8*	96.8 ± 16.6
Mean *Z* score (SD)	0.5 ± 1.4	0.7 ± 1.1	−1.2 ± 1.4*	−0.2 ± 1.2
Maximum post-BD FEV_1/FVC (% pred.), mean ± SD	94.8 ± 8.6	96.0 ± 7.5	86.5 ± 12.8*	93.4 ± 9.4
Mean *Z* score	−0.6 ± 1.2	−0.5 ± 1.0	−1.5 ± 1.4*	−0.8 ± 1.1
Maximum post-BD FEV_1/FVC < LLN, n (%)§	20 (18.0)	14 (18.2)	141* (45.3)	47 (22.1)
FEV_1 BD response (absolute change), mean ± SD	16.4 ± 11.2*	12.7 ± 7.9	12.5 ± 8.2*	11.0 ± 8.1

BD, Bronchodilator; *FEV_1*, forced expired volume in 1 second; *FVC*, forced vital capacity; *SARP*, Severe Asthma Research Program; *SD*, standard deviation.
*$P < .05$ severe vs nonsevere.
†*Z* scores from reference.[10]
‡LLN, lower limits of normal defined by −1.6 *Z* scores.
§% expressed per column.

TABLE III. Features of the SARP III cohort by age and asthma severity: markers of inflammation

	Children (<18 y)		Adults	
	Severe	Nonsevere	Severe	Nonsevere
Sample, n	111	77	313	213
Sputum differential, n	27	17	241	166
Sputum cell count (cells × 10^4/μL), median (min, max)	77.4 (23.7, 153.1)	61.9 (9.5, 199.8)	97.6 (0.0, 195.3)	82.4 (34.9, 187.0)
Sputum eosinophil %, median (min, max)	1.6 (0.0, 53.7)	1.1 (0.0, 61.4)	0.8 (0.0, 63.9)	0.7 (0.0, 59.4)
Sputum neutrophil %, median (min, max)	53.8 (9.4, 90.1)	40.8 (8.3, 80.3)	51.7 (1.5, 99.8)	55.8 (0.5, 99.3)
FeNO (ppb), median (quartiles)	23.0 (12.0, 46.0)	28.0 (12.0, 49.0)	21.0* (13.0, 37.0)	24.0 (16.0, 43.0)
Expired NO > 30 ppb, n (%)†	40 (36.7)	33 (44.0)	96 (31.1)*	87 (40.8)
Serum IgE, median (quartiles)	465 (164, 1207)	490 (151, 834)	163 (45, 384)	141 (46, 374)
At least 1 of 15 positive blood IgE tests, n (%)	104 (94.5)	67 (89.3)	234 (75.2)	173 (82.0)
Number of positive (of 15) allergen-specific IgE tests, median (min, max)	6.0 (3.0, 11.0)	7.0 (3.0, 11.0)	3.0* (0.5, 7.0)	4.0 (2.0, 7.0)
Highly sensitized ≥ 4/15 positive allergen tests, n (%)	74 (67.3)	50 (66.7)	115 (37.0)*	101 (47.9)
Blood eosinophils (%), median (quartiles)	5.4 (2.5, 9.0)	5.6 (3.5, 8.3)	3.0 (2.0, 5.7)	3.0 (2.0, 5.0)
Total blood eosinophils (cells/μL), median (quartiles)	324 (162, 514)	359 (208, 575)	228* (134, 399)	189 (111, 320)
Blood eosinophilia ≥300 cells/μL, n (%)	60 (54.1)	49 (63.6)	120 (38.5)*	60 (28.2)

FeNO, Fraction expired nitric oxide; *SARP*, Severe Asthma Research Program.
*$P < .05$, severe vs nonsevere.
†% expressed per column.

in cross section and then study the effects of advancing age and severity on specific outcomes. We found that children with asthma, regardless of severity, were predominately male with normal body mass and normal lung function, but a relatively high level of blood eosinophilia and allergen sensitization. By contrast, adults with asthma, also regardless of severity, were mostly female, with more obesity and greater airflow limitation. The proportion of enrollees with allergen sensitization was high at all ages, although it was significantly lower in severe asthma by mid-adulthood. The prevalence of airflow limitation was significantly greater with age, and was accompanied by a lower maximum BD response. Standard markers of Th2 inflammation, both allergen sensitization and blood eosinophilia, were significantly lower after childhood.

These results are comparable with the features of severe asthma reported in previous characterization studies.[2-6,15,16] Consistent among these reports, adults with severe asthma typically include a greater proportion of women, and have more symptoms, more exacerbations, and a greater degree of BD-resistant airflow limitation. Generally adults with severe asthma have relatively less allergen sensitization than their nonsevere counterparts, whereas sputum and blood eosinophil counts vary significantly between cohorts. The SARP III cohort is most unique compared with other asthma cohorts in having a

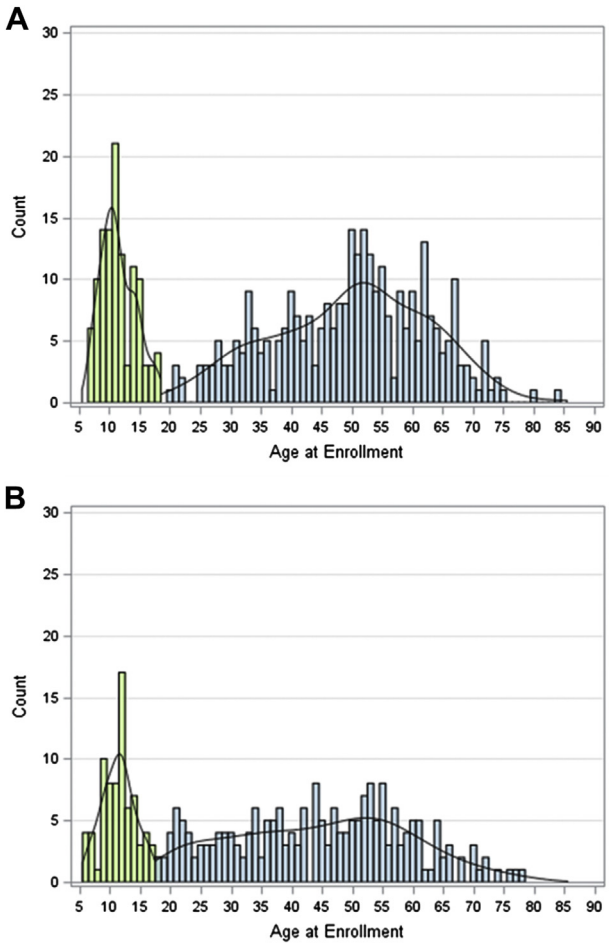

FIGURE 2. Histograms of enrollee counts and age for (**A**) severe and (**B**) nonsevere asthma. Enrollees <18 years of age are shaded in light green. Because of prespecified recruiting goals of 25% children and equal numbers of children between 6-11 years and 12-17 years, comparison of the empirical distributions for severe and nonsevere asthma was limited to adult enrollees shaded in blue ($P = .002$) by the 2-sample Kolmogorov-Smirnoff test.

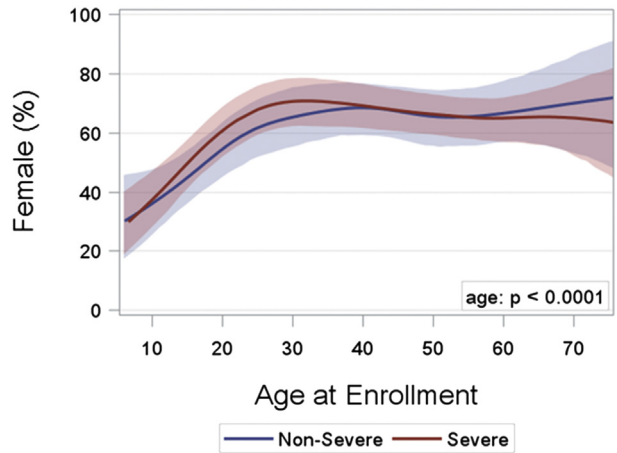

FIGURE 3. Logistic regression curves with cubic splines and bootstrap confidence limits for the percentage of female participants by age and asthma severity. The age effect is significant ($P < .0001$; likelihood ratio test), but the shapes of the curves with age do not differ significantly by severity ($P =$ ns for age by severity interaction).

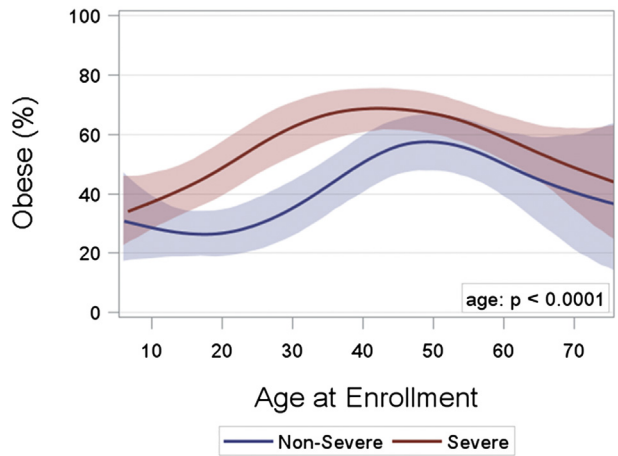

FIGURE 4. Logistic regression curves with cubic splines and bootstrap confidence limits for the percentage of obesity by age at enrollment and asthma severity. The age effect is significant ($P < .0001$; likelihood ratio test), but the shapes of the curves do not differ by severity ($P =$ ns for age by severity interaction).

relatively greater prevalence of obesity and lower sputum eosinophils.[15,16] These findings may be attributable to intrinsic population differences, but also could be due to differences in recruiting practices by study investigators between Europe and the United States. For example, participants with severe asthma in Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes, a large European characterization study, were required to have been under the care of a respiratory physician for at least 6 months preceding enrollment.[16] This was not an inclusion criterion for severe asthma in SARP III, and might account in part for the differences in the 2 cohorts.

A striking finding in the SARP III cohort was a complete reversal of the proportion of males to females after adolescence. This was the case for enrollees with severe and nonsevere asthma. This result has been consistently found in other asthma cohort studies[2,15-17] and has been attributed to a greater degree of bronchial responsiveness in postpubertal females[18] and potential deleterious effects of estrogen and progesterone on lung function[19] and beta adrenergic receptor function.[20] Alternatively, testosterone may confer protective effects on lung function.[21] Sex hormone and lung function changes with puberty will be studied in the longitudinal SARP III protocol so as to better understand the marked change in sex ratio from males to females that occurs after adolescence in asthma.

The prevalence of obesity in the SARP III cohort was higher from childhood to middle age but then was lower after the fifth decade of life. Children had significant variability in BMI but overall children were less obese than adults, wherein the prevalence of obesity in severe adults was nearly 2-fold higher (62% adults vs 38% children). Factors that may explain the relatively high prevalence of obesity in the SARP III sample include the general increase in obesity in the US population and enrichment

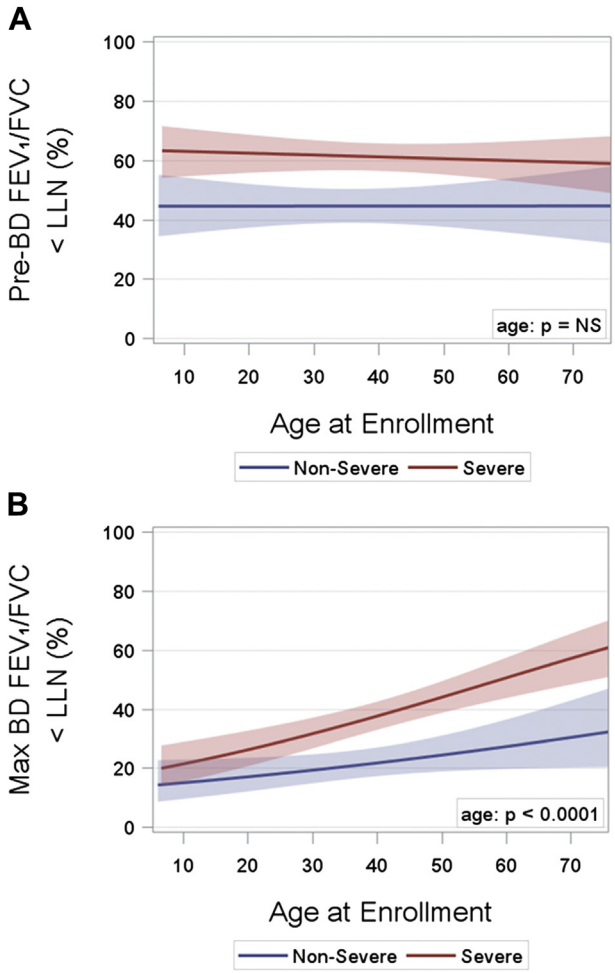

FIGURE 5. **A**, Logistic regression curves and confidence limits for the percentage of pre-BD airflow limitation by age and asthma severity. The age effect is not significant (n= ns; likelihood ratio test). **B**, Logistic regression curves and confidence limits for the percentage of post-BD airflow limitation by age and asthma severity. The age effect is significant ($P < .0001$; likelihood ratio test), but the slopes of the curves do not differ significantly by severity ($P =$ ns for age by severity interaction). *BD*, Bronchodilator; *FEV_1*, forced expired volume in 1 second; *FVC*, forced vital capacity; *LLN*, lower limit of normal.

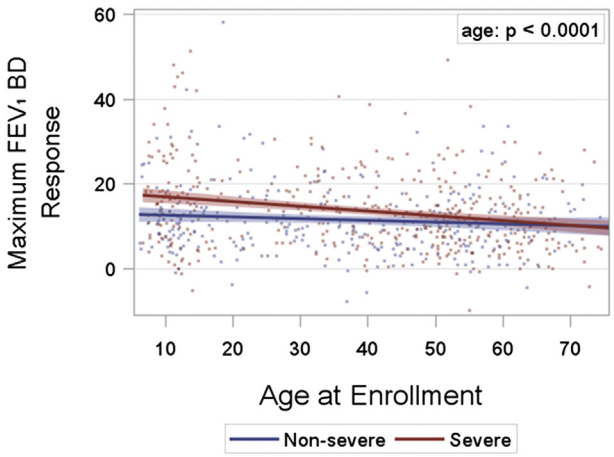

FIGURE 6. Linear regression lines and confidence limits for the absolute change in FEV_1% post-BD by age and asthma severity. The age effect is significant ($P < .0001$; likelihood ratio test), and the slopes differ significantly by severity ($P = .03$; for age by severity interaction). *BD*, Bronchodilator; *FEV_1*, forced expired volume in 1 second.

of the cohort with urban African Americans, a particularly at-risk minority group.[22,23] Obesity appears to predispose adult women more than it does men and appears to be at least as important as an asthma risk factor as the metabolic syndrome, if not more important.[24,25] Understanding of how obesity and metabolic syndrome affect asthma is broadened by the recent finding that metabolic syndrome is associated with more severe asthma but involves only a subset of obese patients.[26]

The prevalence of post-BD airflow limitation in the cohort was significantly higher with advancing age. Whereas post-BD airflow limitation was no different by severity in children, airflow limitation associated with a lower maximum BD response was more common among adults with severe asthma. This was due in part to loss of the maximum BD response, which was significantly lower with advancing age, and the slope of this relationship was steeper in severe versus nonsevere asthma. Differences in lung function with age were highly discordant with age-related differences in markers of Th2 inflammation, which improved as lung function deteriorated. This discordance is the basis for our speculation that alternate mechanisms, supplemental to Th2 inflammation, may favor the progression of airflow limitation with age.

Allergen sensitization, an important phenotypic feature of both severe and non-severe asthma, likewise was informed significantly by advancing age. The downward slope of the proportion of enrollees sensitized to 4 or more allergens with advancing age was particularly steep from childhood to middle age in adults with severe compared with nonsevere asthma. Older age per se is associated with a reduction in the prevalence of allergen sensitization in the general population, both in healthy individuals and those with respiratory disease.[27] Thus a plausible reason for the lower proportions of adults with allergen sensitization in the SARP III cohort could be differential recruitment of more nonallergen sensitized adults compared with children. Likewise we would also consider heterogeneity of the severe asthma phenotype, particularly inclusion of a cluster of adult women identified in SARP I/II[5] and in Europe by Haldar et al[28] with relatively low allergen sensitization but troublesome symptoms refractory to anti-inflammatory therapies. Even though allergen sensitization is lower with age in severe asthma, most adults with severe asthma and nonsevere asthma are allergen-sensitized well into late middle age.

The prevalence of peripheral blood eosinophilia was significantly higher in children than adults but was not differentiated by asthma severity. Although the slope of the prevalence of blood eosinophilia was sharply downward from childhood to middle age, it reached a plateau and then rose from late middle age onward. The relatively low number of enrollees in the sample older than 65 years of age might have skewed this result. Although the overall downward pattern in blood eosinophilia with age appeared to be attenuated in severe asthma, the interaction of age and severity on this outcome was not significant. Because of the relatively low

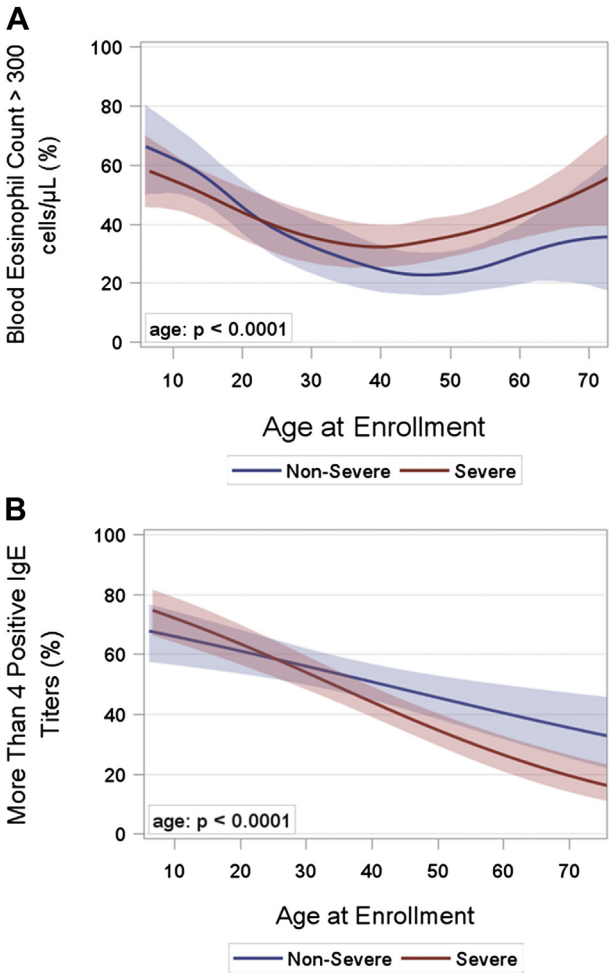

FIGURE 7. A, Logistic regression curves with cubic splines and bootstrap confidence limits for the percentage of enrollees with total blood eosinophil count >300 cells/µL of blood by age and asthma severity. The age effect is significant ($P < .0001$; likelihood ratio test), but the shapes of the curves do not differ significantly by severity ($P =$ ns for age by severity interaction). **B**, Logistic regression curves and confidence limits for the percentage of enrollees with 4 or more positive blood allergen-specific IgE tests by age and asthma severity. The age effect is significant ($P < .0001$; likelihood ratio test). Additionally, the slopes differ by severity ($P = .03$ for age by severity interaction).

number of acceptable sputum samples in children, we did not analyze the effects of advancing age on sputum eosinophilia. A striking feature of the SARP III cohort is the relatively low numbers of sputum eosinophils compared with those seen in severe asthmatics reported in European cohorts.[16,29] We have no ready explanation for this except that it could be attributed to differences in recruiting practices, treatment, and sputum induction/quantification methods.

In the SARP III cohort, FeNO was highest in young adults between 20 and 35 years of age, and was relatively higher in nonsevere than it was in severe asthma. The effects of age on FeNO compared with peripheral blood eosinophilia were strikingly dissimilar, a result that suggests that factors governing the level of FeNO in asthma are different from those governing blood eosinophilia. Although the mechanisms for these differences are unclear, in trials of anti-IL-5, blood eosinophils were reduced without impacting FeNO, and in trials of anti-IL4rα antibodies, FeNO was reduced without decreasing blood eosinophils.[30,31] Mechanisms regulating FeNO include airway buffering capacity,[32] enhanced S-nitrosoglutathione activity,[33] and T-helper I inflammation.[34,35] Other factors that could have independently affected exhaled NO levels in the cohort include corticosteroid use and obesity.[36-38]

In summary, we found significant differences in the baseline phenotypic features of severe and nonsevere asthma in children and adults. Whereas children with asthma tend to be males with normal weight and lung function in the context of eosinophilia and frequent allergen sensitization, adults with asthma have more obesity and are more heterogeneous with regard to measures of lung function, eosinophilia, and allergen sensitization. Among adults with asthma, increasing age is significantly associated with greater airflow limitation, a decline and then greater eosinophilia by late middle age, and less allergen sensitization. Age-related differences in features affected by asthma severity were limited to the maximum BD response, allergen sensitization, and FeNO. The greatest number of enrollees in the SARP III cohort with severe asthma were in middle age, suggesting that gender effects, obesity, and novel immune perturbations that occur more commonly in middle age inform the severe asthma phenotype.

Acknowledgments

The authors acknowledge the contributions of the study coordinators and staff at each of the clinical centers and the Data Coordinating Center as well as all the study participants that have been integral to the success of the Severe Asthma Research Program. Spirometers used in SARP III were provided by nSpire Health (Longmont, Colo). The authors appreciate the support of the Scientific Program Officers at the National Heart, Lung and Blood Institute (Dr. Patricia Noel, Dr. Tom Croxton, and Dr. Robert Smith) and input from the members of the Data Safety and Monitoring Board.

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ONLINE REPOSITORY

METHODS

Recruiting methods

The Severe Asthma Research Program (SARP) III cohort was assembled in response to a National Institutes of Health (NIH) mandate (RFA HL-11-018, June 11, 2010) requesting applications for clinical centers to establish a severe asthma research program that outlined specific recruiting methods. Clinical centers and a data coordinating center were named and a broad recruiting process was initiated targeting a sample enriched in severe asthma (60%) and including 30% minorities, 50% women, and 25% children. Study coordinators at each clinical site screened potential enrollees with both severe and nonsevere asthma by various methods including program notices on the ClinicalTrials.gov web site, data queries of patients with asthma receiving care at the respective clinical sites, research databases of patients available for clinical trials, social media, advertisements in local media, and archives of patients who had participated previously in SARP I/II.

Maximum bronchodilator response

The threshold maximum bronchodilator response for entry into the SARP III cohort was a $\geq$12.5% increase in forced expired volume in 1 second (FEV_1) % predicted compared with the prebronchodilator value. A total of 15 children (8% of the total) and 33 adults (6% of the total) qualified according to this threshold but had <200 mL absolute change in FEV_1.

Allergen-specific IgE blood tests

These included *Dermatophagoides pteronyssinus* D1, *Dermatophagoides farinae* D2, Cat dander e1, Dog dander E5, German cockroach (*Blattella germanica*) i6, *Alternaria alternata* m6, *Cladosporium herbarum* m2, *Aspergillus fumigatus* M3, Timothy grass (or grass mix) gx2, Short ragweed W1, Common weed mix: cocklebur, lambs quarter, pigweed, English plantain, Russian thistle Wx5, Tree mix: oak, elm, maple, willow, cypress Tx4, Tree mix: box elder, birch, beech, oak, walnut Tx6, Mouse urine proteins E72, and Rat urine protein E74.

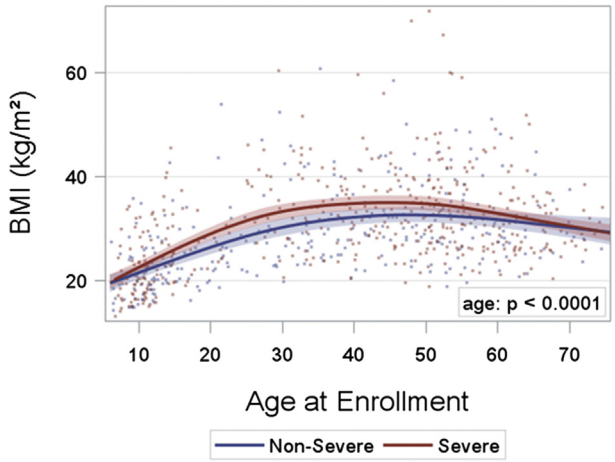

FIGURE E1. Nonlinear regression curves with cubic splines and bootstrap confidence limits for body mass index (BMI, kg/m^2) by age and asthma severity. The age effect is significant ($P < .0001$; *F*-test), but the shapes of the curves do not differ significantly by severity ($P =$ ns; age by severity interaction).

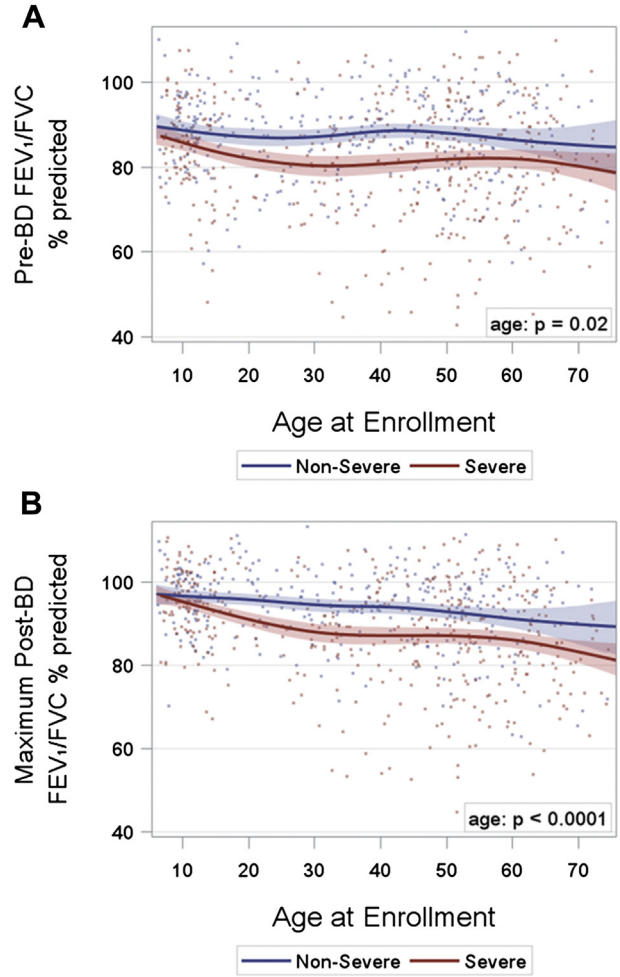

FIGURE E2. **A**, Nonlinear regression curves with cubic splines and confidence limits for pre-BD FEV$_1$/FVC % predicted by age and asthma severity. **B**, Nonlinear regression curves with cubic splines and confidence limits for the maximum post-BD FEV$_1$/FVC % predicted by age and asthma severity. The age effect is significant ($P = .02$ and $P < .0001$) for both pre- and post-BD FEV$_1$/FVC % predicted, respectively. However, the shapes of the curves for each plot do not differ significantly by severity ($P =$ ns for age by severity interaction). *BD*, Bronchodilator; *FEV$_1$*, forced expired volume in 1 second; *FVC*, forced vital capacity.

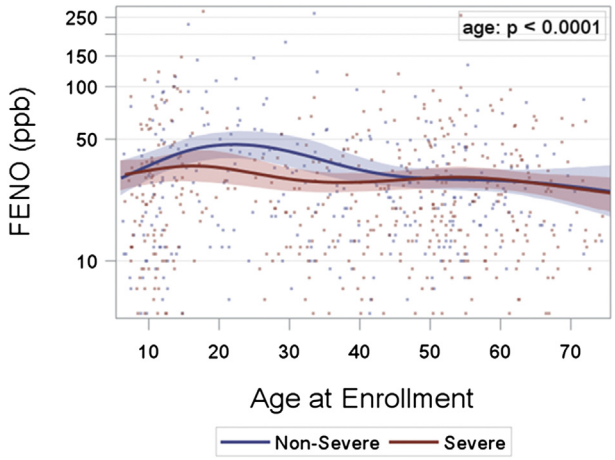

FIGURE E3. Poisson regression curves with cubic splines and bootstrap confidence intervals for FeNO by age and asthma severity. The age effect is significant ($P < .0001$; likelihood ratio test), and the shapes of the curves differ significantly by severity ($P < .0001$ for age by severity interaction). *FeNO,* Fraction expired nitric oxide.

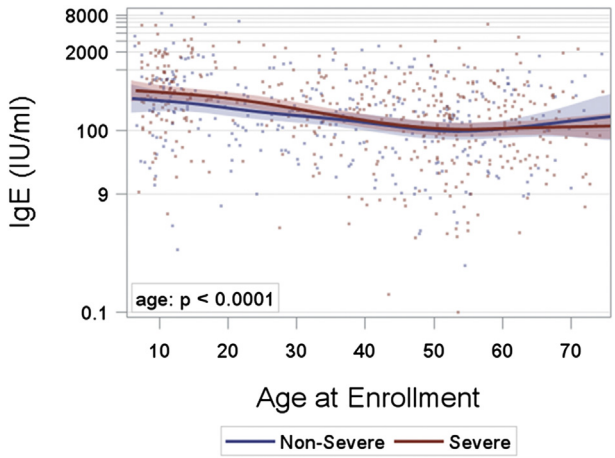

FIGURE E4. Poisson regression curves and cubic splines with confidence intervals for total serum IgE by age of enrollment and asthma severity. The age effect is significant ($P < .0001$; likelihood ratio test), but the shapes of the curves do not differ significantly by severity ($P =$ ns for age by severity interaction).

TABLE E1. SARP III study cohort: inclusion and exclusion criteria

Inclusion criteria
• Physician diagnosis of asthma
• Age 6 y and older
• Bronchodilator reversibility $\geq$12%, or airway hyperresponsiveness reflected by a methacholine $PC_{20} \leq 16$ mg/mL
Exclusion criteria
• No primary medical caregiver
• Pregnancy (if undergoing methacholine challenge or bronchoscopy)
• Current smoking
• Smoking history >10 pack years or >5 pack years if <30 y of age
• Other nonasthmatic chronic pulmonary disorders
• History of premature birth <35 wk estimated gestational age
• Evidence the participant or family may be unreliable or poorly adherent to asthma treatment or the study procedures
• Known relocation plans away from the clinical center before study completion
• Any criterion that places the participant at unnecessary risk according to the judgment of the principal investigator and/or attending physicians of record

PC_{20}, Provocation concentration of methacholine to decrease the FEV_1 by 20% from baseline; *SARP*, Severe Asthma Research Program.

TABLE E2. SARP III longitudinal protocol schedule of visits and procedures

	Base line	Steroid response		Longitudinal protocol					
	V1	V2	V3	6 mo	V4 12 mo	18 mo	V5 24 mo	30 mo	V6 36 mo
Scheduling window		14 d	18 ± 3 d	±90 d	±90 d	±90 d	±90 d	±90 d	±90 d
Consent/eligibility	X								
Questionnaires	X	X	X	X	X	X	X	X	X
PE/VS/BMI/tanner stage	X				X		X		X
Spirometry	X	X	X		X		X		X
Max bronchodilator	X	X	X		X		X		X
Methacholine	X								
Pregnancy test	X	X	X		X		X		X
Sputum induction		X	X		X				
FeNO		X	X		X		X		
CBC		X							
Immunocap		X							
Triamcinolone Rx		X							

BMI, Body mass index; *CBC*, complete blood count; *FeNO*, fraction expired nitric oxide; *PE*, physical examination; *SARP*, Severe Asthma Research Program; *VS*, vital signs.

TABLE E3. Proportions of adult and pediatric SARP enrollees by asthma severity and ICS dose range

SARP phenotype group	Adult	Pediatric	Total
1. Mild intermittent: base $FEV_1 \geq 80\%$, no ICS	29	10	39
	5.51	5.32	
2. Mild persistent: base $FEV_1 \geq 80\%$, low-med ICS	64	34	98
	12.17	18.09	
3. Untreated moderate: base $FEV_1 < 80\%$, no ICS	23	2	25
	4.37	1.06	
4. Moderate persistent: base $FEV_1 < 80\%$, low-med ICS	74	11	85
	14.07	5.85	
5. Meets 2013 ERS/ATS criteria for severe asthma	313	111	424
	59.51	59.04	
Undefined phenotype: $FEV_1 \geq 80\%$, controlled "severe" asthma	10	10	20
	1.9	5.32	
Undefined phenotype: $FEV_1 \geq 80\%$, high current ICS	5	7	12
	0.95	3.72	
Undefined phenotype: $FEV_1 < 80\%$, high current ICS	8	3	11
	1.52	1.6	
Total	526	188	714

ATS, American Thoracic Society; *ERS*, European Respiratory Society; FEV_1, forced expired volume in 1 second; *ICS*, inhaled corticosteroid; *SARP*, Severe Asthma Research Program.

TABLE E4. Features of ineligible vs enrolled participants in SARP III

	Ineligible N = 234	Enrolled N = 714
Gender		
Male n (%)	76 (32)	291 (41)
Female n (%)	158 (68)	423 (59)
Race		
White n (%)	159 (68)	408 (57)
Black n (%)	39 (17)	213 (30)
Other n (%)	36 (15)	93 (13)
Ethnicity		
Hispanic n (%)	18 (8)	47 (7)
Non-Hispanic n (%)	216 (92)	667 (93)
Median age (quartiles)	44 (26, 59)	41 (17, 54)

SARP, Severe Asthma Research Program.